Two-year drug survival of dupilumab in a large cohort of difficult-to-treat adult atopic dermatitis patients compared to cyclosporine A and methotrexate

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Published in:
Allergy

DOI:
10.1111/all.14324

Publication date:
2020

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

DOI: 10.1111/all.14324

Two-year drug survival of dupilumab in a large cohort of difficult-to-treat adult atopic dermatitis patients compared to cyclosporine A and methotrexate: Results from the BioDay registry

To the Editor,

Dupilumab is a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor subunit α (IL-4 Rα), the common subunit of the type 2 cytokines IL-4 and IL-13, blocking signaling of both cytokines and consequently inhibiting the entire Th2 pathway.[1] Overall, the clinical efficacy and safety of dupilumab ± topical corticosteroids

TABLE 1 Patient and treatment characteristics for treatment with dupilumab, cyclosporine A, and methotrexate

	Dupilumab (n = 402)	Cyclosporine A (n = 356)	Methotrexate (n = 89)
Female, n (%)	157 (39.1)	167 (46.9)	36 (40.4)
Age (y), mean (±SD)	43.3 (15.8)	37.6 (14.2)	50.1 (17.3)
History of prior treatment with oral immunosuppressive drugs, n (%)	400 (99.5)	69 (19.4)	62 (69.7)
Treatment duration (mo), [a]median (IQR)	15.1 (8.2-20.3)	7.9 (3.2-14.4)	7.3 (3.0-11.4)
Status of use, [c]n (%)			
Active	358 (89.1)	80 (22.5)	37 (41.6)
Discontinued	37 (9.2)	258 (72.4)	45 (50.5)
Lost to follow-up	7 (1.7)	18 (5.1)	7 (7.9)

[a]Data lock two years after start treatment; dupilumab 15-12-2019; cyclosporine A 01-01-2014; methotrexate 01-02-2015.

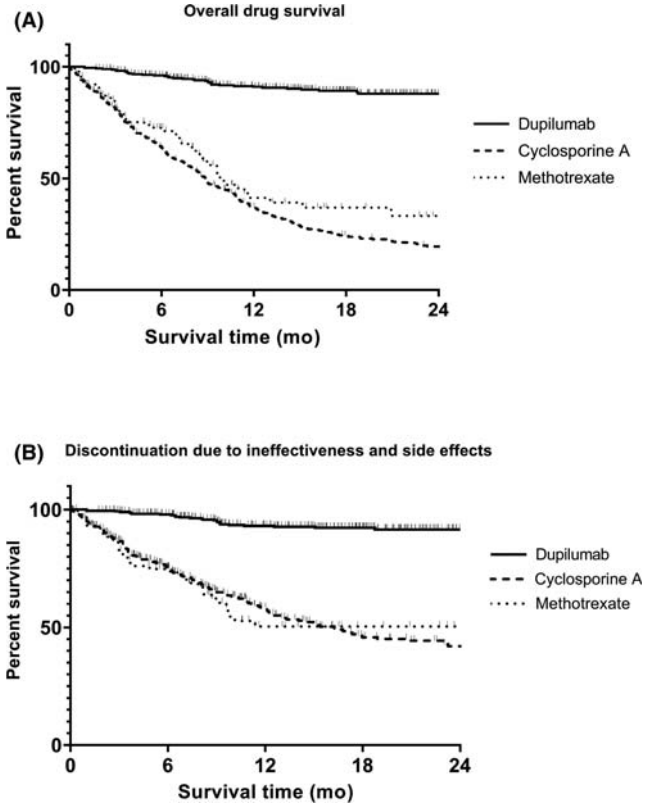

FIGURE 1 A, Overall drug survival for dupilumab, cyclosporine A, and methotrexate. B, Drug survival related to discontinuation due to treatment failure for dupilumab, cyclosporine A, and methotrexate

(TCS) have been demonstrated in several phase 3 clinical trials for the treatment of patients with moderate-to-severe AD.[2] In clinical trials, efficacy of dupilumab is tested under ideal circumstances in selected patients, and therefore, results are not always generalizable to daily practice. Recent results from dupilumab treatment in daily practice show a clinically relevant improvement of physician-reported outcome measures and patient-reported outcome measures after 3-6 months, which is in line with data from clinical trials.[3,4]

Drug survival is an analysis which gives a reflection of daily practice by analyzing the time from initiation to discontinuation of therapy. Drug survival is a comprehensive outcome covering effectiveness, safety, and patients' and doctors' preferences.[5] Drug survival studies for dupilumab are scarce, and studies comparing drug survival of dupilumab with conventional oral immunosuppressive drugs for AD are lacking.[6] In the current study, we primarily aim to assess the drug survival of dupilumab, and secondarily to compare drug survival of dupilumab with other oral immunosuppressive drugs (cyclosporine A (CsA) and methotrexate (MTX)) in two historical (previously published) daily practice cohorts of moderate-to-severe AD patients before the introduction of dupilumab.[7,8] Patients treated with dupilumab were included in the BioDay registry, a prospective multicenter registry that contains daily practice data on the effectiveness and safety of dupilumab for the treatment of AD, including both quality of life (QoL) as well as clinical parameters. Patients were treated with MTX, CsA, and dupilumab according to national guidelines concerning dosage and follow-up. Drug survival was determined through Kaplan-Meier survival curves and analyzed for overall drug survival (discontinuation due to well-controlled disease; side effects [with/without ineffectiveness]; ineffectiveness [with/without side effects]; and other) for dupilumab, CsA, and MTX and separately for treatment failure (ineffectiveness combined with side effects). Patients, who were using dupilumab/CsA/MTX at time of data lock or were lost to follow-up, were censored. For each patient, data on treatment duration and reason for discontinuation were collected, as well as other detailed patient and treatment characteristics.

The dupilumab cohort comprised of 402 patients (39.1% female, mean age 43.3 years) with a median dupilumab treatment duration of 15.1 (interquartile range (IQR) 8.2-20.3) months at time of data lock (480 active treatment years) (Table 1). In the dupilumab cohort, 99.5% had a history of prior treatment with oral immunosuppressive drugs (93.8% CsA, 33.8% MTX, 22.9% azathioprine, 16.9% enteric-coated mycophenolate sodium) compared to 19.4% in the CsA and 69.7% in the MTX cohort.

At the moment of data lock, 358 patients (89%) used dupilumab, 37 patients (9%) had discontinued dupilumab treatment, and

7 patients (2%) were lost to follow-up. The most frequent reason for discontinuation of dupilumab was side effects (17 patients (4%)). Seven patients (2%) discontinued treatment because of ineffectiveness, two patients (0.5%) due to a combination of both side effects and ineffectiveness (Table S1). Regarding CsA, 356 patients were included with a median treatment duration of 7.9 (IQR 3.2-14.4) months. The majority of the patients (n = 258 (73%)) discontinued treatment within two years after start of CsA, mostly because of well-controlled disease (n = 79(22%)) followed by side effects (n = 72 (20%)).[8] The MTX cohort included a total of 89 patients with a median treatment duration of 7.3 (IQR 3.0-11.4) months. Half of the patients (n = 45 (51%)) discontinued treatment after two years of follow-up, 22 patients (25%) due to side effects, and 13 patients (15%) due to ineffectiveness.[7]

The overall drug survival rates for dupilumab were 91% and 88% after 1 and 2 years, respectively. In CsA-treated patients, drug survival rates were 37% and 20%. This was comparable to the drug survival of MTX, which was 41% and 33%, after, respectively, 1 and 2 years. Drug survival of dupilumab was significantly longer compared to MTX and CsA ($P < .0001$) (Figure 1A). Approximately, half of the patients discontinued CsA and MTX because of treatment failure (ineffectiveness and/or side effects); limited dupilumab patients discontinued treatment due to treatment failure (Figure 1B). Due to the low number of patients discontinuing dupilumab treatment, a prediction analysis of drug survival was not possible in the present study.

A drug survival rate of 89% after 800 days (26.3 months) of treatment with dupilumab in a daily practice cohort (n = 112) of AD patients treated at a tertiary care center in the United States (US) was reported by Khosravi et al Reasons for discontinuation were AD flare (5/112 (5%)), conjunctivitis (3/112 (3%)), and adequate control with phototherapy (1/112 (1%)).[6] Overall drug survival rates were comparable with the results of our study, although we found a slightly lower rate of discontinuation due to ineffectiveness (2% vs 5%).

Drug survival is influenced by the availability of alternative treatment options and changes in the population treated over time. None of patients were previously treated with dupilumab. Patients included in the MTX and CsA cohort were treated before initiation of clinical trials and marketing authorization of dupilumab, and therefore, the availability of dupilumab did not influence the drug survival in these cohorts. Longer drug survival of dupilumab (compared to MTX and CsA) can be explained by a persistent clinical response and lack of discontinuation due to controlled disease, but also due to the lack of availability of alternative treatment options.

In conclusion, this study shows that dupilumab has a longer drug survival compared to CsA and MTX. Only a limited number of dupilumab patients discontinued treatment due to side effects and/or ineffectiveness. Future daily practice data will provide further important information on the impact of the introduction of new biologic agents and small molecules for the treatment of AD on drug survival of dupilumab.

CONFLICT OF INTEREST

MS de Bruin-Weller reports grants and other from Sanofi-Genzyme/Regeneron, during the conduct of the study; grants and other from Sanofi-Genzyme/Regeneron, other from AbbVie (advisory board member), other from Eli Lilly (advisory board member), other from Pfizer (advisory board member), other from Galderma (advisory board member), other from UCB(advisory board member), and other from Leo Pharma (advisory board member), outside the submitted work; M de Graaf reports grants and other from Sanofi-Genzyme/Regeneron, during the conduct of the study; grants and other from Sanofi-Genzyme/Regeneron and other from Eli Lilly (advisory board member), outside the submitted work; M. Kamsteeg reports personal fees from participation in the advisory board of Sanofi in 2017, outside the submitted work; MLA Schuttelaar has received honoraria for lecturing and is an advisory board member for Sanofi-Genzyme; received consultancy fees from Regeneron Pharmaceuticals; and is an advisory board member for Leo Pharma and Eli Lilly. The other authors have nothing to disclose.

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SUPPORTING INFORMATION

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DOI: 10.1111/all.14326

Association of rhinovirus species with nasopharyngeal metabolome in bronchiolitis infants: A multicenter study

To the Editor,

Bronchiolitis is the leading cause of hospitalization in US infants.[1] The majority of severe bronchiolitis (requires hospitalization) is caused by respiratory syncytial virus (RSV) and rhinovirus (RV).[1] RVs are RNA viruses with >160 recognized genotypes that are classified into three species (A, B, and C).[2] While bronchiolitis is traditionally considered a single disease entity and currently available treatment does not differ by viral etiology,[1,3] recent studies suggest heterogeneity of bronchiolitis by infecting virus.[4] Indeed, research has shown that RSV and RV species are associated not only with different acute (eg, disease severity)[1] and chronic (eg, incident asthma)[5] morbidity burdens, but also with different airway microbiota profiles.[6] Despite the clinical and research importance, it remains unclear how different RV species perturb the downstream functional molecules that influence clinical phenotypes in infants with bronchiolitis. Metabolomics address this knowledge gap through comprehensively profiling metabolites that are a function of the child's genetic architecture and environmental factors,[1] such as respiratory viruses. In this study, we investigated the relationships between respiratory viruses (including different RV species) and nasopharyngeal metabolome in infants with severe bronchiolitis.

This is an analysis of data from the 35th Multicenter Airway Research Collaboration (MARC-35) cohort study—a multicenter prospective cohort study of infants with severe bronchiolitis. The details of the study design, measurements, and analysis are described in the Online Supplement. Briefly, we enrolled 1016 infants (aged <1 year) hospitalized with bronchiolitis—according to the American Academy of Pediatrics guidelines[3]—in 17 sites across 14 US states (Table S1). Investigators collected nasopharyngeal samples within 24 hours of hospitalization using a standardized protocol.[7] These samples underwent (a) real-time PCR to test for respiratory viruses, with subsequent RV genotyping at the University of Wisconsin—Madison, and (b) liquid chromatography-tandem mass spectrometry to profile the metabolome. In the current analysis, we grouped infants into three mutually exclusive virus categories: RSV-only (reference), RV-A, and RV-C. In the primary analysis, we excluded RV-B infection because of its clinical insignificance[1] and fewer number of cases. We compared the detected metabolites between RSV and RV-A as well as between RSV and RV-C groups. To account for high-order nonlinear correlations between metabolites, we fit random forest models and determined 30 metabolites with largest between-group difference for the downstream analyses. We then tested for the association of viruses with each metabolite level by fitting multivariable linear regression models with multiple test adjustment. Next, using graphical modeling approach, we inferred the underlying relationship between respiratory viruses, patient's age, corticosteroid use, and metabolites from the cross-sectional data. To detect biologically meaningful pathways, we also performed a pathway analysis (metabolite set enrichment analyses). Lastly, we fit multivariable logistic regression models to examine the association